

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 33-43, 46, 47, 51, 52, 58-61, 71, 76, and 79-83 are pending in the application, with 33, 42, 46, 58, and 79 being the independent claims. New claims 80-83 are sought to be added. Support for new claims 80-82 is found in the specification at page 23, line 15 to page 24, line 2. Support for new claim 83 is found at page 26, line 7 to page 29, line 2. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under 35 U.S.C. § 112, second paragraph

A. First Rejection (Claim 59)

Claim 59 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]he last compound listed in claim 59 has $R_6 = CF_3$ and $R_9 =$ hydrogen. There is no antecedent basis for this limitation in the parent claim 58, which does not allow for $R_9 =$ hydrogen."

Applicants respectfully disagree. The last compound has been deleted from claim 59. Thus, claim 59 is not indefinite.

B. Second Rejection (Claim 61)

Claim 61 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite (Office Action, page 3). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]he last compound listed in claim [61] has $R_6 = ClCH_2$ and $R_9 =$ hydrogen. There is no antecedent basis for this limitation neither in the either parent claim 60 nor in grandparent claim 58, which does not allow for $R_9 =$ hydrogen."

Applicants respectfully disagree. The last compound has been deleted from claim 61. Thus, claim 61 is not indefinite.

Applicants respectfully submit that the rejections of claims 59 and 61 under 35 U.S.C. § 112, second paragraph has been traversed, accommodated or rendered moot. Therefore, Applicants respectfully submit that these rejections should be withdrawn.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 33-43, 46, 47, 51, 52, and 76 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification, "while being enabling for treating breast and cervical carcinomas, does not reasonably provide enablement for treating all other claimed cancers or inflammatory diseases." (Office Action, page 3). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that there is a large degree of experimentation. Applicants respectfully disagree. While the testing of the identified compounds for efficacy for each of the listed diseases may be time consuming, it is not undue experimentation. One of skill in the art of cancer chemotherapy or treatment of immune diseases routinely carries out the described testing in a straightforward and reliable manner. The testing of large numbers of compounds in assays known to correlate with clinical efficacy is regularly carried out by the skilled artisan. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983). The Examiner has not provided any reason to show why such experimentation would be undue.

The Examiner alleges that the specification merely states Applicants' intention to treat cancer and inflammatory diseases without sufficient details or working examples. Applicants respectfully disagree. The present specification describes the treatment of cancers and immune disorders in sufficient detail for one of skill in the art to carry out the claimed methods. It is well known to those of skill in the art what are the symptoms of these disorders and how the disorders may be treated as these disorders have been known and treated for many years by the skilled artisan. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). The specification describes pharmaceutical formulations in detail. The fact that there is no working example of a formulation is not indicative of a lack of enablement, as the preparation of pharmaceutical formulations is well known in the art. The skilled artisan could readily determine appropriate doses for the claimed compounds using routine methods

for testing potency *in vitro* and *in vivo*, including the assays described in the specification at pages 55-61.

The Examiner has found the treatment of breast and cervical carcinomas to be enabled, based in part on the assay results disclosed on pages 58-61 of the specification. It is pointed out that the effect of the disclosed compounds on Jurkat cells was also demonstrated (Examples 72 and 73). Jurkat cells are human T-lymphoblasts. Thus, evidence is presented to show that the disclosed compounds are capable of inducing apoptosis in T cells, and therefore capable of treating T cell-related cancers (*e.g.*, leukemia, lymphoma) and T cell-mediated immune disorders (*e.g.*, inflammation, psoriasis, autoimmune lymphoproliferative syndrome). The present claims are limited to the specified diseases. The Examiner has provided no data or references to show that the disclosed compounds are not expected to be effective for treating the other claimed diseases that are not exemplified. Furthermore, even if one or two of the listed diseases is not treatable by the disclosed compounds, the presence of inoperative embodiments within the scope of a claim does not render the claim non-enabled as long as the skilled artisan can determine those embodiments that are operative and inoperative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 U.S.P.Q. 409, 414 (Fed Cir. 1984). Here, the testing of the disclosed compounds on the limited list of claimed diseases is carried out using tests routinely used in the art of disease therapy, so the skilled artisan could readily determine operative and inoperative embodiments.

The Examiner indicated that there is no working example of treatment of any disease in man or animals. The presence of working examples is not required to show enablement. Furthermore, the Examiner pointed out in the Office Action that the testing of compounds

in an assay known to be correlated to clinical efficacy of treatment is sufficient for enabling a method of treating a disease, and indeed has indicated that the treatment of breast and cervical carcinomas is enabled based on the disclosed *in vitro* assay results. Thus, there are working examples in the present specification.

The Examiner cites Talanian to allege that inhibitors of caspase-1 might be useful to treat the inflammatory disease sepsis, whereas the present compounds are activators of caspases and may make sepsis worse. Applicants point out that the caspase family includes caspases known to be involved in cytokine maturation (such as caspase-1) and other caspases involved in apoptosis (see Talanian, page 273). While the specific inhibition of caspase-1 to prevent production of interleukin-1 β may treat sepsis, as suggested by Talanian, the activation of apoptosis-related caspases such as 3, 6, and 7 by the present compounds will lead to cell death. The death of inflammatory cells by apoptosis, including cells that normally produce interleukin-1 β , will in effect inhibit the production of interleukin-1 β . Thus, induction of apoptosis will be effective for the treatment of inflammation.

The Examiner cites Miller to allege that it is unknown if blockage of caspase activity is therapeutically meaningful. This reference is irrelevant insofar as it discusses the inhibition of caspases whereas the present invention involves the activation of caspases. Furthermore, the statement by Miller merely relates to the fact that it is unclear if the specific inhibition of a single caspase will have an effect since multiple caspases are likely to be activated during an apoptotic stimulus. Since the presently claimed method likely involves the activation of multiple caspases, Miller's point is not relevant.

The Examiner is of the opinion that the scope of the claims is very broad.

Applicants acknowledge that the claims encompass a large number of potential compounds.

However, in discussing genus claims, the M.P.E.P. states that:

representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

(M.P.E.P. 2164.02). Here, the specification discloses 30 compounds within the claimed genus that have been tested for activity and two of the active compounds have been further shown to be active in assays that are correlative with *in vivo* success in treating disease. In the face of this evidence, the Examiner has failed to provide adequate reasons why the skilled artisan could not use the claimed genus as a whole without undue experimentation.

Applicants respectfully submit that the rejection of claims 33-43, 46, 47, 51, 52 and 76 under 35 U.S.C. § 112, first paragraph has been traversed, accommodated or rendered moot. Therefore, Applicants respectfully submit that this rejection should be withdrawn.

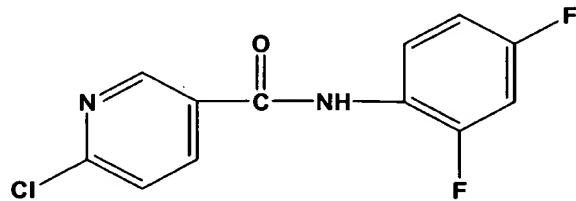
Rejections Under 35 U.S.C. § 102

A. First Rejection (Claim 58)

Claim 58 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Mantlo (Office Action, page 7). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that:

[t]here are still three compounds in this reference that anticipate Applicants' claims. The compound shown below fits Formula (III) with $R_1 = R_3 =$ fluorine, $R_9 =$ chlorine, and $R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} =$ hydrogen. It has Registry Number 224817-04-3. Lines 32-34, column 84 of the reference states that 6-chloro-nicotinamides were used to prepare the compounds of Tables 8-11. The compound shown below therefore was used to make the entries of lines 28-45, column 86. The compound with $R_1 = R_3 =$ methoxyl was used form the entries spanning columns 86 and 87. The compound with $R_1 =$ hydrogen and $R_3 =$ fluorine was used to make the entries in lines 45-58, column 87. The compound with $R_{11} =$ methyl and $R_3 =$ chlorine was used to make the entries in lines 37-54, column 88.



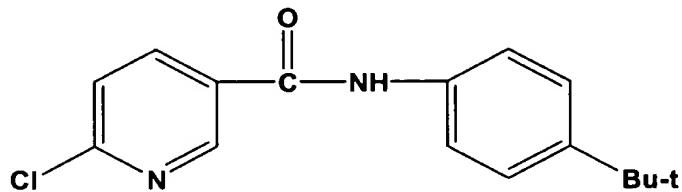
(Office Action at page 7).

Applicants respectfully disagree. Mantlo discloses compounds in which R_1 and/or R_5 is fluorine, methoxy, or hydrogen. In contrast, the compounds of the rejected claim require that at least one of R_1 and R_5 be NO_2 , cyano, alkyl, or haloalkyl. Therefore, Mantlo does not anticipate claim 58. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

B. Second Rejection (Claims 58 and 71)

Claims 58 and 71 were rejected under 35 U.S.C. § 102(b) as being anticipated by Von der Saal (Office Action, page 7). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that: "[t]he compound shown below fits Formula III with $R_1 = R_3 = t\text{-butyl}$, $R_9 = \text{chlorine}$, and $R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} = \text{hydrogen}$. It has Registry Number 125125-27-1 and is found in Example 35, lines 43-51, page 10 of the reference. Compositions are taught in claim 5 of the reference. Thus, claim 71 is anticipated."



(Office Action at pages 7-8).

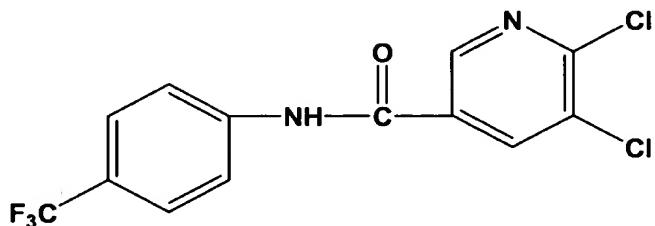
Applicants respectfully disagree. Von der Saal discloses a compound in which R_1 and R_5 are hydrogen. In contrast, the compounds of the rejected claims require that at least one of R_1 and R_5 be NO_2 , cyano, alkyl, or haloalkyl. Therefore, Von der Saal does not anticipate claims 58 and 71. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

C. Third Rejection (Claim 58)

Claim 58 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Setliff (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]here are two compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with $R_3 = \text{CF}_3$, $R_9 = R_{10} = \text{chlorine}$, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} = \text{hydrogen}$. It has

Registry Number 150115-54-1. The other compounds has R_3 = fluorine, $R_9 = R_{10}$ = chlorine, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11}$ = hydrogen and has Registry Number 150115-51-8."



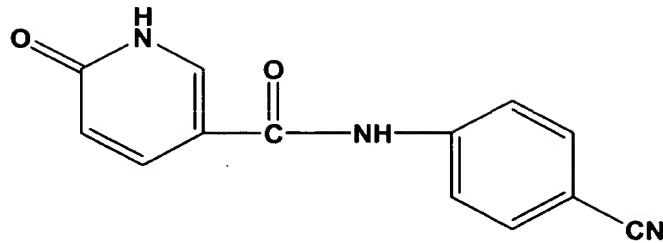
(Office Action at page 8).

Applicants respectfully disagree. Setliff discloses compounds in which $R_1 = R_5$ = hydrogen. In contrast, the compounds of the rejected claim require that at least one of R_1 and R_5 be NO₂, cyano, alkyl, or haloalkyl. Therefore, Setliff does not anticipate claim 58. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

D. Fourth Rejection (Claim 58)

Claim 58 has been rejected 35 U.S.C. § 102(b) as being anticipated by Austel (Office Action, page 8). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]he compound shown below fits formula (III) with R_3 = cyano, R_9 = hydroxyl, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11}$ = hydrogen. It has Registry Number 149354-21-2 and is found in lines 24-52, column 35 of the reference. Please note that the compound is drawn in its' tautomeric keto form."



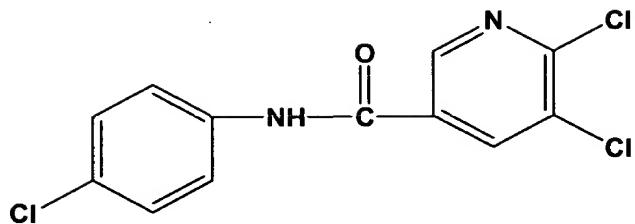
(Office Action at pages 8-9).

Applicants respectfully disagree. Austel discloses a compound in which $R_1 = R_5 =$ hydrogen. In contrast, the compounds of the rejected claim require that at least one of R_1 and R_5 be NO_2 , cyano, alkyl, or haloalkyl. Therefore, Austel does not anticipate claim 58. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

E. Fifth rejection (Claim 58)

Claim 58 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Persons (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]here are three compounds in this reference that anticipate Applicant's claims. The compound shown below fits formula (III) with $R_3 = R_9 = R_{10} =$ chlorine, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} =$ hydrogen. It has Registry Number 165539-62-8. The other two compounds have Registry Numbers 150115-51-8 and 150115-54-1. . ."



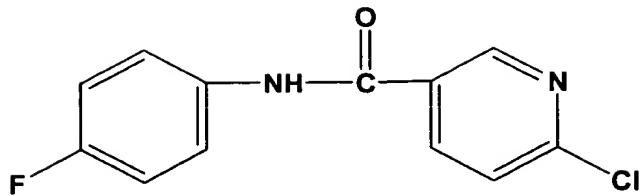
(Office Action at page 9).

Applicants respectfully disagree. Persons discloses a compound in which $R_1 = R_5$ = hydrogen. In contrast, the compounds of the rejected claim require that at least one of R_1 and R_5 be NO_2 , cyano, alkyl, or haloalkyl. Therefore, Persons does not anticipate claim 58. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

F. Sixth rejection (Claim 58)

Claim 58 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Setliff (Office Action, page 9). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]here are two compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with R_3 = fluorine, R_9 = chlorine, R_{10} = fluorine, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{11} =$ hydrogen. It has Registry Number 179330-70-2. The other compound has $R_3 = CF_3$, $R_9 =$ chlorine, $R_{10} =$ fluorine, and $R_1 = R_2 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} =$ hydrogen. It has Registry Number 179330-73-5. . ."



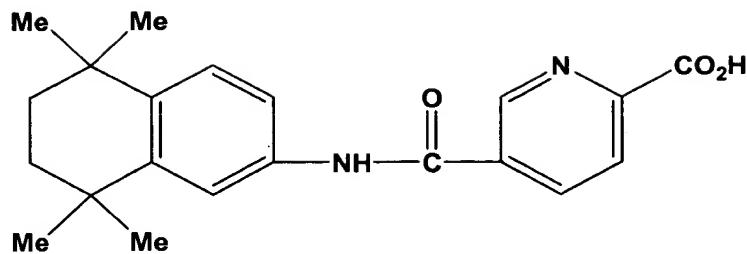
(Office Action at pages 9-10).

Applicants respectfully disagree. Setliff discloses compounds in which $R_1 = R_5 =$ hydrogen. In contrast, the compounds of the rejected claim require that at least one of R_1 and R_5 be NO_2 , cyano, alkyl, or haloalkyl. Therefore, Setliff does not anticipate claim 58. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

G. Seventh rejection (Claims 33-35, 42, and 46)

Claims 33-35, 42, and 46 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Shudo (Office Action, page 10). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]here are four compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with $R_2 = R_3 =$ fused carbocycle substituted by methyl, $R_9 =$ carboxy, and $R_1 = R_4 = R_5 = R_6 = R_7 = R_{10} = R_{11} =$ hydrogen. It has Registry Number 150115-54-1. Treatment of leukemia is taught in the abstract. . ."



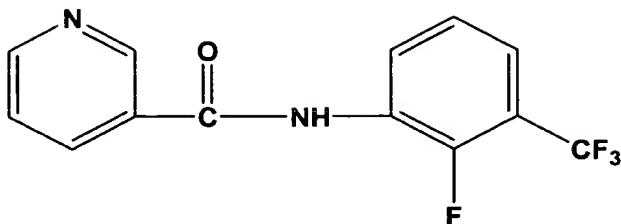
(Office Action at pages 10-11).

Applicants respectfully disagree. Shudo discloses compounds in which R₉ or R₁₀ is carboxy or carboxymethyl. Claim 33 as amended does not encompass carboxy or carboxymethyl in the definition of R₉ or R₁₀. Therefore, Shudo does not anticipate claims 33-35, 42, and 46. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

H. Eighth rejection (Claims 33, 36, and 38)

Claims 33, 36, and 38 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Klebanov (Office Action, page 11). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]here are eight compounds in this reference that anticipate Applicants' claims. The compound shown below fits formula (III) with R₄ = CF₃, R₅ = fluorine, and R₁ = R₂ = R₃ = R₆ = R₇ = R₉ = R₁₀ = R₁₁ = hydrogen. It has Registry Number 69135-93-9. Treatment of inflammation is taught in the abstract. . ."



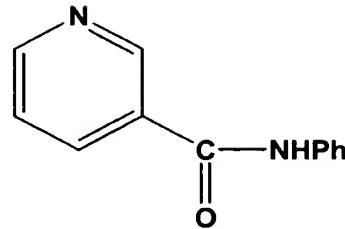
(Office Action at page 11).

Applicants respectfully disagree. Klebanov discloses compounds in which R₂ or R₃ is haloalkyl or haloalkoxy. Claim 33 as amended does not encompass haloalkyl or haloalkoxy in the definition of R₁-R₅. Therefore, Klebanov does not anticipate claims 33, 36, and 38. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

I. Ninth rejection (Claims 33, 36, and 38)

Claims 33, 36, and 38 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Bukhtiarova (Office Action, page 11). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]he compound shown below fits formula (III) with R₁ = R₂ = R₃ = R₄ = R₅ = R₆ = R₇ = R₈ = R₁₀ = R₁₁ = hydrogen. It has Registry Number 69135-90-6. Treatment of inflammation is taught in the abstract. . ."



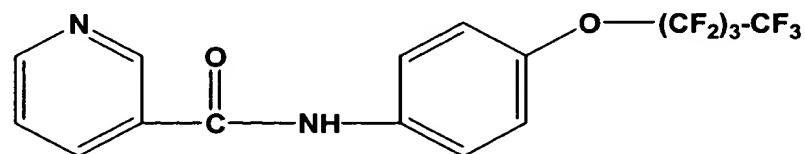
(Office Action at pages 10-11).

Applicants respectfully disagree. Bukhtiarova discloses compounds in which R₁ is hydrogen. Claim 33 as amended does not encompass hydrogen in the definition of R₁. Therefore, Bukhtiarova does not anticipate claims 33, 36, and 38. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

J. Tenth rejection (Claims 33, 36, and 38)

Claims 33, 36, and 38 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Miryan (Office Action, page 12). Applicants respectfully traverse this rejection.

The Examiner is of the opinion that "[t]he compound shown below fits formula (III) with R₃ = the haloalkoxy group pentafluoroethoxy and R₁ = R₂ = R₄ = R₅ = R₆ = R₇ = R₉ = R₁₀ = R₁₁ = hydrogen. It has Registry Number 69135-90-6. Treatment of edema and exudate is taught in the abstract. Both edema and exudate are a form of inflammation. . ."



(Office Action at page 12).

Applicants respectfully disagree. Miryan discloses a compound in which R₃ is haloalkoxy. Claim 33 as amended does not encompass haloalkoxy in the definition of R₁-R₅. Therefore, Miryan does not anticipate claims 33, 36, and 38. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Date: October 10, 2003

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